REMARKS

With entry of this amendment, claims 1, 3, 12 and 13 are pending. Claims 1 and 3 have been amended to overcome the indefiniteness rejection. New claims 12 and 13 were added to recite specific features of the claimed mouse and method that were removed to overcome the indefiniteness rejection. The amendments are supported throughout the specification, in particular as noted below. No new matter has been added. Reconsideration is requested.

Claims 1 and 3 were rejected under 35 USC § 112, second paragraph, as being indefinite. It was the Examiner's view that the terms "substitution" and "deficiency" were indefinite, and furthermore that the expression "such as destruction, deficiency, or substitution" was superfluous. The expression "such as destruction, deficiency, or substitution" has been deleted, thereby rendering this portion of the rejection moot. New dependent claims 12 and 13 recite that the mutation is a deletion or substitution. These claims are supported throughout the specification, and in particular at page 6, lines 3-4. It is respectfully submitted that the term "destruction" rather than "deletion" to refer to a gene is a translation error. The Examiner also stated that the term "amount" in claim 3 was unclear because it was not clear whether the term refers to the degree of severity of each symptom or to the number of symptoms present at any degree of severity. The claim has been amended to recite "severity of at least one of said symptoms", which is supported at page 8, in the paragraph beginning at line 10. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1 and 3 have been rejected under 35 USC §103 as being obvious over **Kalluri et al. (1997)** and **Kalluri et al. (1994)** and **Abbate** in view of **Takai** and **Yuasa et al**. This rejection is traversed for the following reasons.

It is the Examiner's view that Kalluri et al (1997) taught immunizing various strains of wild-type mice with the α3(IV) NC1 antigen from type IV collagen, leading to high titers of α3(IV) NC1 antibodies that bind to the type IV collagen in kidney basement membrane and lungs. The Examiner further states that that Abbate taught immunizing wild-type rats with α3 type IV collagen causing experimental Goodpasture's syndrome and Kalluri (1994) taught

immunizing rabbits with the NC1 subdomain of α3 type IV collagen and using the model mouse to test for new forms of therapy. The Examiner acknowledges that neither Kalluri (1997) nor Abbate nor Kalluri (1994) taught using an FcγRIIB knockout mouse in making a model of Goodpastures or using type IV collagen rather than subunits of type IV collagen.

According to the Examiner's view, Takai taught knocking out the FcγRIIB gene in mice results in increased humoral and anaphylactic responses in the mice in response to antigens and that the FcγRIIB gene encodes a low-affinity immunoglobulin-G receptor. The Examiner then states that Yuasa taught that the FcγRIIB knockout mice of Takai exhibited collagen induced arthritis in response to immunization with type II collagen, that **Kalluri (1995)** taught that antisera from some Goodpasture's patients also bind to α1(IV) collagen and α4(IV) collagen in addition to α3(IV) collagen. According to the Examiner, it would have been obvious to immunize the FcγRIIB knockout mice taught be Takai and by Yuasa with a type IV collagen antigen as taught by Kalluri (1994), by Abbate and by Kalluri (1997) to result in the present invention.

Comparison of the present invention and the citations

Kalluri (1997, J. Clin. Invest. 100: pages 2263-2275) discloses a mouse model for Goodpastures syndrome obtained by immunizing a wild type mouse with α3(IV) NC1 domains. There is no suggestion of the use of a mouse in which the FcγRIIB gene has been rendered deficient.

Abbate (1998, Kidney International, Vol. 54, pages 1550-1561) discloses the animal model using a rat, not a mouse as in described in claims 1 and 3. As Abbate's animal model shows extremely weak alveolar hemorrhage, it is difficult to distinguish from other nonspecific inflammation images and the model is not appropriate for use. Also, the weakness of symptoms of alveolar hemorrhage and inflammation images leads difficulty in distinguishing from nonspecific bleeding or inflammation which is induced from immunological adjuvant itself in rare cases. Therefore Abbate's animal model is not appropriate for the Goodpasture's syndrome animal model.

Kalluri (1994, PNAS, Vol. 91, pages 6201-6205) discloses that Goodpasture's syndrome animal model obtained by being immunized with recombinant proteins shows weak alveolar hemorrhage, and hence are far from satisfactory to be used as an appropriate animal model pulmonary lesion of Goodpasture's syndrome which is often lethal to humans. That is, a detailed consideration of Kalluri has revealed that, as described in the abstract of the citation, the target autoantigen in Goodpasture's syndrome is α3 (IV), one of the genetically different six α strands that constitute type IV collagen. Its epitope localizes in non-collagen domain (NC1) of α3 strand and immunizing with α3 (IV) NC1 dimer from bovine kidney will cause autoimmune diseases in a rabbit, while immunizing with α strand of type IV collagen other than α3 strand will not cause any autoimmune diseases. Also, immunizing with α3 (IV) NC1 hexamer, although it is an α3 strand, will not cause any autoimmune diseases. In this manner, the mechanism of the development of autoimmune diseases is complex and whether autoimmune diseases are actually induced is unknown unless each case is tested by actually running an experiment even if the same type IV collagen or the same part of such collagen is used.

Takai (1996, Nature, Vol. 379, pages 346-348) discloses a method of producing a FcγRIIB receptor deficient mouse and the regulation system of Type I allergy. However, as the Examiner acknowledges, there is no suggestion regarding immunization with Type IV collagen and no disclosure regarding Goodpasture's syndrome nor Goodpasture's syndrome animal model.

Yuasa et al. (1999, J. Exp. Med. 189, pages 187-194) describes that about 50 % of FcγRIIB knockout mice of H-2b haplotype, which are generally considered not to induce arthritis, developed collagen-induced arthritis (CIA), which is an autoimmune disease, when immunized with type II collagen. However, there is no suggestion that FcγRIIB knockout mice are useful as Goodpasture's syndrome animal model.

First, it is respectfully submitted that there would have been no motivation for a person of skill in the art to combine the teachings of Takai and Yuasa, which use a knock-out mouse and do not mention Goodpasture's syndrome, with those of Kalluri and Abbate, which use a wild-type mouse and rat, respectively, and are directed to producing a model for Goodpasture's syndrome, to obtain the present invention. The teachings of Yuasa are directed to producing a mouse model for collagen induced arthritis, and a person of skill in the art would not have been motivated to combine this reference with those of Kalluri and Abbate to produce a mouse model for Goodpasture's syndrome.

The present inventors actually immunized FcγRIIB knockout mice with other target antigens, and no autoimmune diseases were caused. More specifically, the present inventors immunized FcγRIIB knockout mice with bovine type I collagen and bovine type III collagen which are the target antigens in SLE (systemic lupus erythematosus) and neither significant difference between serum antibody titers of anti-bovine collagen IgG1 antibody and IgG2a antibody nor the apparent pathological lesion was observed (see Reference Figure 1, appended to the present amendment). In addition, the present inventors immunized FcγRIIB knockout mice with human desmoglein 3 (DSG 3) and mouse desmoglein 3, the target antigens in pemphigus vulgaris, and no autoimmune diseases were caused. The present inventors further immunized FcγRIIB knockout mice with bovine GM-CSF, the target antigen in alveolar proteinosis, and in this case also no autoimmune diseases were caused.

As described in Example 1, type IV collagen (pH 8.0) was used to produce Goodpasture's syndrome model mouse of the present invention. The reasons type IV collagen was used include that: 1) it is affordable; 2) it is highly homologous among human, bovine, and mouse; 3) it is conceivable that being a self component, the mouse collagen may not be recognized as an antigen upon immunization and may fail to cause immune responses. However, as to the reason why the mice immunized with type IV collagen from bovine was induced to develop autoimmune diseases, the mechanism is not known clearly.

Production of Goodpasture's syndrome animal model according to the method described in the above Kalluri citation requires preparation of α3 (IV) NC1 dimer from bovine kidney, which is expensive and time-consuming. Moreover, the produced

Goodpasture's syndrome animal model shows weak alveolar hemorrhage, and hence is far from satisfactory to be used as an appropriate animal model for pulmonary lesion of Goodpasture's syndrome which is often lethal to humans. In contrast, the Goodpasture's syndrome animal model according to the present invention can be produced by immunizing FcγRIIB knockout mice with type IV collagen which is an antigen available commercially (and is more convenient compared to recombinant collagen). The Goodpasture's syndrome model mouse produced according to the present invention is the animal model which exhibits the most severe alveolar hemorrhage ever demonstrated, as well as glomerulonephritis. (This model mouse exhibited significant alveolar hemorrhage, but if the mouse had been immunized with recombinant collagen, almost no alveolar hemorrhage would have been caused). Also, by immunizing with bovine collagen, antibody against mouse collagen, that is, autoantibody, can be induced. Thus, Applicants submit that the present invention is highly useful as Goodpasture's syndrome animal model. In addition, the pathological lesion is caused dependently on autoantibody against type IV collagen, which is induced by immunization. In consequence, Applicants submit that animal model of the present invention shows all the characteristics of human Goodpasture's syndrome, that is, alveolar hemorrhage, glomerulonephritis, and the antikidney glomerular basement membrane antibody, and is highly practical as novel disorder animal model whose symptom closely resembles that of the actual human disorder.

It is respectfully submitted that the Examiner has based this rejection on hindsight, which is not a proper basis for a 35 USC §103 rejection. For this reason, withdrawal of the rejection is respectfully requested.

Furthermore, even if the prior combination would have been obvious, which Applicants strongly deny, the currently claimed model mouse and method have unexpected advantages as mentioned above, a basis for overcoming any perceived obviousness. The currently claimed mouse model, which has three phenotypes, showing the severe symptom of the Goodpasture's syndrome would not have been predictable, even if the five references of Kalluri, Abbate Takai, and Yuasa are taken into consideration together. For this reason, withdrawal of the rejection is respectfully requested.

In conclusion, it is respectfully submitted that claims 1 and 3 are not obvious in view of the cited references. Reconsideration and withdrawal of the rejection under 35 USC § 103 are respectfully requested.

All rejections having been addressed, it is respectfully submitted that this application is in condition for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

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